



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 33/24	A1	(11) International Publication Number: WO 95/11033 (43) International Publication Date: 27 April 1995 (27.04.95)
<p>(21) International Application Number: PCT/AU94/00641</p> <p>(22) International Filing Date: 21 October 1994 (21.10.94)</p> <p>(30) Priority Data: PM 1950 22 October 1993 (22.10.93) AU</p> <p>(71) Applicant (for all designated States except US): COMMON-WEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION [AU/AU]; Limestone Avenue, Campbell, ACT 2602 (AU).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): WEIGOLD, Helmut [AU/AU]; 54 Leeds Road, Mont Waverley, VIC 3149 (AU).</p> <p>(74) Agents: CORBETT, Terence, G. et al.; Davies Collison Cave, 1 Little Collins Street, Melbourne, VIC 3000 (AU).</p>		<p>(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).</p> <p>Published With international search report.</p>
<p>(54) Title: POLYOXOMETALLATES IN THE TREATMENT OF FLAVIVIRUS INFECTIONS</p> <p>(57) Abstract</p> <p>Pharmaceutical compositions containing polyoxometallates and pharmaceutically acceptable derivatives thereof. The use of such compounds or compositions in therapy for the treatment or prophylaxis of infections by viruses which are confirmed or probable members of the family Flaviviridae including Hepatitis C.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

POLYOXOMETALLATES IN THE TREATMENT OF FLAVIVIRUS INFECTIONS

ANTIVIRAL AGENTS

5

The present invention relates to pharmaceutical compositions containing polyoxometallates and pharmaceutically acceptable derivatives thereof, and to the use of these compounds in therapy for the treatment or prophylaxis of infections by viruses which are confirmed or probable members of the family Flaviviridae, for example
10 infections such as yellow fever, dengue fever, Australian encephalitis, Japanese encephalitis and Hepatitis C.

Flaviviruses are well known to be the causative agents of a number of human diseases including the most important arthropod-borne viral afflictions of mankind -
15 dengue, yellow fever, and Japanese encephalitis. In addition, eight flaviviruses cause disease in domestic or wild animals of economic importance. Yellow fever and dengue fever are widespread and well known as mosquito borne diseases of tropical countries. There are between 30 and 60 million flavivirus infections per year including one million Japanese encephalitis infections. The extent of Hepatitis C is not known with any degree
20 of certainty because an infection can exist for many years without the patient being aware of the symptoms. Hepatitis C produces a much higher rate of chronic liver infection than Hepatitis B which is a recognised hazard in many countries. About 50% of patients develop chronic infections, compared with 5 to 10% of those infected with Hepatitis B. Chronic infection causes cirrhosis of the liver, impairs liver function, and
25 20-30 years later causes liver failure. It has been estimated that the rate of infection approaches and may exceed 1% of the population in Australia. There is no proven cure or vaccine for Hepatitis C.

Effective vaccines are available for some viruses only, eg for yellow fever,
30 Japanese encephalitis and tick-borne encephalitis. Treatment of dengue fever and Australian encephalitis relies on the patient's own immune defences; infections can be fatal.

- 2 -

An antiviral drug to control infections with flaviviruses is thus highly desirable. Drugs which control or inhibit replication have proven to be effective in the control of some other viruses. However, because of the difficulty of inhibiting viruses while leaving the non-infected cells unimpaired, few antiviral drugs are currently in widespread
5 clinical use.

The family *Flaviviridae* is a newly-recognised large group (in excess of 70 species) of small, enveloped viruses that contain a single strand of positive-sense RNA of 10 kilobases. As a consequence of the difficulty mentioned above and recent
10 recognition of flaviviruses as a unique group with a unique replication strategy, no attention has been paid to antiviral compounds to control flaviviral infections.

All members of the family *Flaviviridae* possess a unique replication strategy which is inhibited by the compositions of this invention. The non-structural genes NS3
15 and NS5 which have been proposed to be involved in replication share a great deal of sequence similarity between species, and hence an inhibitor of replication should be active against all flaviviruses.

Prior Art

20 Heteropolytungstate compounds have been known for over 100 years. Most of their applications stem from their redox chemistry and also their high ionic weights and charges. Their redox chemistry has lead to their use as catalysts for the oxidation of organic substrates such as, for example, propylene to acrylic acid, ethylene to acetaldehyde. In the biological field heteropolytungstates have found use as electron
25 dense stains for electron microscopy, as analytical reagents for proteins and several have also been shown to inhibit viral DNA and RNA polymerases (J. C. Cherman, *et al.*, *Biochem. Biophys. Res. Commun.*, 1975, 65, 1229; M. Hervé, *et al.*, *ibid*, 1983, 116, 222.).

30 The heteropolytungstates within the scope of this invention include the Keggin and Dawson (also known as the Wells-Dawson) type structures and compounds based on these structures in which one or more of the tungsten atoms are removed and, in the majority of cases, exchanged by other metal atoms. Vacancies in the structures are most

- 3 -

- often created by the extraction of WO^{4+} or $\text{W}_3\text{O}_6^{6+}$ from the Keggin ($\text{XW}_{12}\text{O}_{40}^{n-}$) or Dawson ($\text{P}_2\text{W}_{18}\text{O}_{62}^{6-}$) species. Isomers of these unsaturated (lacunary) polyanions are possible, a consequence of the location of the vacancy. (R. Massart R. Contant, J. M. Fruchart, J. M. Ciabrini, M. Fournier, *Inorg. Chem.* 1977, 16, 2916; T. L. Jorris, M. Kozik, N. Casan-Pastor, P. J. Domaille, R. G. Finke, W. K. Miller and L. C. W. Baker, *J. Am. Chem. Soc.* 1987, 109, 7402; T. J. R. Weakley, *Polyhedron* 1987, 6, 931; R. Contant and J.-P. Ciabrini, *J. Chem. Res. (S)*, 1977, 222; R. G. Finke, M. W. Droege and P. J. Domaille, *Inorg. Chem.*, 1987, 26, 3886; M. T. Pope, "Heteropoly and Isopoly Oxometalates", Springer-Verlag, Berlin, 1983.) The position of the vacancy in
- 10 $\text{P}_2\text{W}_{17}\text{O}_{61}^{10-}$ is defined by the prefix α_1 - for a belt vacancy or β_2 - for a cap vacancy. The rotation of W_3 -oxide triads in the structures leads to a number of isomers. Thus a 60° rotation of a W_3 triad cap can convert, for example, an α - isomer to the β - isomer. In the trivacant polyanions of the type $\text{XW}_9\text{O}_{34}^{n-}$, A- or B-forms are obtained, depending upon whether a corner-linked W_3 oxide triad is lost (A-form) or an edge-
- 15 linked W oxide triad has been removed (B-form).

- Unsaturated heteropolyanions can behave as ligands by bonding, at their vacant site, with metal ions. These metal ions, when not sterically crowded, can carry ligands such as water, organic coordinating species or organometallic groups. Organometallic
- 20 moieties can also react with exposed oxygen atoms on, for example, trisubstituted Keggin or Dawson structures (R. G. Finke and M. W. Droege, *J. Am. Chem. Soc.*, 1984, 106, 7274 and R. G. Finke, B. Rapko and P. J. Domaille, *Organometallics* 1986, 5, 175). An oxygen atom on the Keggin structure can also be alkylated with reagents such as trimethyloxonium salts (W. H. Knoth and R. L. Harlow, *J. Am. Chem. Soc.* 1981,
- 25 103, 4265). Some of the oxygen atoms on heteropolytungstates can also be exchanged for fluorine atoms (F. Chauveau, P. Doppelt and J. Lefebvre, *Inorg. Chem.* 1980, 19, 2803; T. L. Jorris, M. Kozik and L. C. W. Baker, *Inorg. Chem.* 1990, 29, 4584).

- Other heteropolyanion species are formed by reaction of two $\text{W}_5\text{O}_{18}\text{H}^{5-}$ ions with
- 30 metal ions such as the lanthanoids (R. D. Peacock and T. J. R. Weakley, *J. Chem. Soc. A*, 1971, 1836). Heteropolyanions having PW_7 phosphotungstate groups, generally bridged by phosphate group(s), are known (J. Fuchs and R. Palm, *Z. Naturforsch.* 1988,

- 4 -

43b, 1529 and R. Acerete, J. Server-Carrio, A. Vegas and M. Martinez-Ripoll, *J. Am. Chem. Soc.*, 1990, 112, 9386).

5 The central atom in the compounds can vary widely, especially in the case of the simpler Keggin type structures. The central atom in the Dawson type structures is most often phosphorus.

Polyoxometallates containing metals such as molybdenum, niobium and vanadium have also been made.

10

We have now made the unexpected discovery that polyoxometallate polyanions are active against viruses belonging to the *Flaviviridae* family. In particular they inhibit the replication of such viruses stopping the development of an infection.

15 Accordingly the present invention provides compositions for use in the treatment or prophylaxis of a flavivirus associated infection having as active ingredient one or more polyoxometallate compounds selected from formula 1 to 17 below or a pharmaceutically acceptable derivative thereof. The compounds of the invention are polyanions with associated cations (A) for electrical neutrality. They crystallize with a
20 variable number of molecules of water of crystallization dependent upon the conditions of product recovery and subsequent treatment; all such hydrates come within the scope of this invention.

By "a pharmaceutically acceptable derivative" is meant any pharmaceutically
25 acceptable salt, or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) a compound of the invention or an active metabolite or residue thereof.

The pharmaceutical compositions of the present invention may comprise an effective
30 amount of one or more compounds selected from Formulae 1-17 in association with one or more pharmaceutically acceptable carriers or diluents, and optionally other therapeutic agents. Each carrier must be pharmaceutically "acceptable" in the sense of being compatible with the other ingredients of the composition and not injurious to the patient.

- 5 -

It should be understood that in addition to the ingredients particularly mentioned, the compositions of this invention may include other agents conventional in the art having regard to the type of composition in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavouring agents.

Compositions include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

The present invention also extends to a method for the treatment or prophylaxis of a flavivirus associated infection, which comprises the administration of a composition containing an effective amount of one or more compounds selected from Formulae 1-17.

The compounds may be prepared by the literature methods or adaptations thereof, varying reactants and conditions as required to obtain the target compound. General review articles, describing the preparation, structure and properties of many of the compounds, include P. Souhay, *"Ions Minéraux Condensés"*, Masson, Paris, 1969; M. T. Pope, *"Heteropoly and Isopoly Oxometalates"*, Springer-Verlag, Berlin, 1983; T. J. R. Weakley, *Structure and Bonding*, Springer-Verlag, Berlin, 1974, 18, 131; M. T. Pope and A. Müller, *Angew. Chem. Int. Ed. Engl.* 1991, 30, 34.

The compounds of the invention useful as active ingredients, are listed as Formulae 1-17 below along with appropriate methods of preparation for each sub-type. In each formula, A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule.

- 6 -



$M \neq M'$ and $M = W, V, Mo$; $M' = V, Mo$.

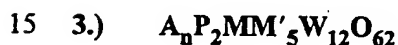
The compounds were obtained by the reactions of M. Abbessi, R Contant, R. Thouvenot, and G. Hervé, *Inorg. Chem.* 1991, 30, 1695 and/or for $M = Mo$, the reactions of R. Contant and J.-P. Ciabrini, *J. inorg. nucl. Chem.* 1981, 43, 1525.



$M, M' = V, Mo$.

10

The compounds were obtained by the reactions of M. Abbessi, R Contant, R. Thouvenot, and G. Hervé, *Inorg. Chem.* 1991, 30, 1695 and/or for $M = Mo$, the reactions of R. Contant and J.-P. Ciabrini, *J. inorg. nucl. Chem.* 1981, 43, 1525.



$M = W$; $M' = Mo$ or $M = M' = Ti, Mo, Fe, V$

The compounds with $M = W$ were prepared according to R. Contant and J.-P. Ciabrini, *J. inorg. nucl. Chem.* 1981, 43, 1525. The compounds ($M = M'$) $M = Mo$ were made following R. Contant and J.-P. Ciabrini, *J. Chem. Research (M)* 1977, 2601; the compounds $M = Ti$ were made by the method of P. D. Savage and B. R. C. Theobald described in British Patent Appl. No. 70944/91.



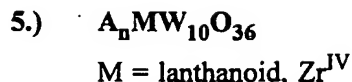
25 $X = P^V, Si^{IV}, Ge^{IV}$

R = an organic residue or one containing an organometallic, metal carbonyl or metal coordinated with a ligand.

$M = Ge^{IV}, Si$

30 The compounds were made following the methods of W. H. Knoth, *U.S. Patent* (1980) 4,196,136; W. H. Knoth, *J. Am. Chem. Soc.* 1979, 101, 2211; M. S. Weeks, C. L. Hill, and R. F. Shinazi, *J. Med. Chem.* 1992, 35, 1216.

- 7 -



The compounds were prepared according to the method of R. D. Peacock and T. J. R. Weakley, *J. Chem. Soc. A*, 1971, 1836. The structure of the Ce^{IV} compound $Na_6[Ce^{IV}(W_5O_{18}H)_2]$ has been determined by J. Iball, J. N. Low and T. J. R. Weakley, *J. Chem. Soc. Dalton Trans.*, 1974, 2021.



The compounds were prepared following A. Tézé and G. Hervé, *Inorg. Synth.*, 1990, 27, 88. (Ed. A. P. Ginsberg) Wiley-Interscience.



The compounds were prepared following R. Contant, *Inorg. Synth.* 1990, 27, 108. (Ed. A. P. Ginsberg) Wiley-Interscience, or R. Contant and J.-P. Ciabrini, *J. Chem. Research (M)* 1977, 2601.

20



The compounds were prepared following R. Contant, *Inorg. Synth.* 1990, 27, 110. (Ed. A. P. Ginsberg) Wiley-Interscience; R. Contant and A. Tézé, *Inorg. Chem.* 1985, 24, 25 4610.



The compounds were made following the procedures of J. Fuchs and R. Palm, *Z. Naturforsch.* 1988, 43b, 1529 and that of R. Thouvenot, A. Tézé, R. Contant and G. Hervé, *Inorg. Chem.* 1988, 27, 524.

- 8 -

10.) $A_nNaP_5W_{30}O_{110}$

The compounds based on Pressler's anion were made by the procedure described by M. H. Alizadeh, S. P. Harmalker, Y. Jeannin, J. Martin-Frère and M. T. Pope, *J. Am. Chem. Soc.* 1985, 107, 2662.

11.) $A_nP_6W_{18}O_{79}$

The compounds were made following the procedures of J. Fuchs and R. Palm, *Z. Naturforsch.* 1988, 43b, 1529 and R. Acerete, J. Server-Carrio, A. Vegas and M. Martinez-Ripoll, *J. Am. Chem. Soc.*, 1990, 112, 9386.

12.) $A_nLn_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4$

Ln = lanthanoid metal ion.

15

Synthesised following H. Naruke and T. Yamase, *J. Lumin.* 1991, 50, 55.

13.) $A_nP_4W_{30}Nb_6O_{123}$ 20 $A_nSi_2W_{18}Nb_6O_{77}$

These compounds were made by the method of D. J. Edlund *et al.*, *Organometal.* 1988, 7, 1692; R. G. Finke *et al.*, *J. Amer. Chem. Soc.*, 1984, 106, 7274.

25 14.) $A_nPV_{14}O_{42}$

These compounds were made according to the methods of F. Preuss and H. Schug, *Z. Naturforsch.* 1976, 31b, 1585; R. Kato, A. Kobayashi and Y. Sasaki, *J. Am. Chem. Soc.* 1980, 102, 5671.

30

15.) $A_nPV_{13}O_{41}$

These compounds were made according to the methods of F. Preuss and H. Schug, *Z. Naturforsch.* 1976, 31b, 1585.

5

16.) Zirconium containing heteropolytungstates.

The structures of these novel compounds are not known and the structures postulated are based primarily on the metal analysis of the products, physical properties when available and, at times, the nature of the starting materials. It is noted that the ^{31}P nmr signals
10 obtained from the zirconium containing compounds are often broad and complex. The cations in these products, as is the case for most polyoxometalates, can be exchanged for other cations using, for example, an appropriate ion exchange resin.

Preparation of compound 16/1

15

This compound was prepared by reaction of $Na_{10}[\alpha-SiW_9O_{34}].aq.$ 14.2 g (5 mmol) with 4.8 g (15 mmol) $ZrOCl_2 \cdot 8H_2O$ in 100 mL H_2O at $70^\circ C$ for 4 h. After filtration through Celite filter aid, 25 g KCl was added to give a white precipitate. The mixture was warmed and the precipitate became a clear dense phase which on cooling
20 to room temp. and scratching with a glass rod gave a white solid (10.2 g). This was redissolved in 50 mL H_2O at $65^\circ C$ and reprecipitated on addition of 10 g KCl. This was collected, dissolved in 30 mL H_2O at $70^\circ C$, filtered hot and let stand at room temp. The somewhat soft product was collected and washed with ethanol to give a white solid (6.8 g). The metal analyses, %W 52.2; %Zr 10.1; %K 5.03, corresponded to
25 $W_{18}Zr_{7.02}K_{8.15}$. A possible structure for 16/1 may be based on a dimer; two $[Zr_3SiW_9O_{38}(H_2O)_2]^{6-}$ units connected through a Zr^{4+} .

Preparation of compound 16/2.

30 On reaction of $Na_{10}[\alpha-SiW_9O_{34}].aq.$ 7.1 g (2.5 mmol) with 1.46 g (5 mmol) finely powdered Cp_2ZrCl_2 in 50 mL H_2O at room temp. overnight a yellow, slightly turbid solution was obtained. After treatment with activated charcoal 10 g KCl was added. The off-white precipitate formed was collected, washed with ethanol and air

- 10 -

dried to give 5.1 g product. It was redissolved in 200 mL H₂O at 80°C to give a pale yellow solution from which a pale yellow powder (3.4 g) was obtained on treatment with 10 g KCl. Analyses: %W 55.34, %Zr 6.92, %K 6.96; corresponding to an atomic ratio for the compound of W₂₀Zr_{5.04}K_{11.8}. A possible structure for 16/2 may be one similar to that postulated for 16/1, ie one in which two [Zr₂W₁₀SiO₄₀]⁸⁻ units are joined through a Zr⁴⁺. IR spectrum (KBr disc, cm⁻¹) 997(w), 934(m), 895(s), 792(sh), 755(s).

Preparation of compound 16/3.

10 This product was obtained by treatment of 100 mmol Na₂WO₄·2H₂O with 10 mmol Na₂SiO₃·5H₂O and ca. 7 mmol acetic acid in 100 mL H₂O at room temp followed by addition of 20mmol Cp₂ZrCl₂ and stirring the solution (yellow) for several days. It did not decolourise on treatment with carbon. Addition of excess KCl gave a white precipitate which was dissolved in H₂O at 60 - 70°C. The white compound that
15 separated on cooling to room temp. was collected and air dried. Analysis; %W 49.61; %Zr 6.34; %Si 0.76; %K 6.25; corresponding to an atomic ratio for the compound of W₂₀Zr_{5.15}Si_{2.01}K_{11.8}, which is similar to that found for 16/2. Based on their ir spectra, the compounds are not identical. Ir spectrum (KBr disc, cm⁻¹) 998 (sh), 954(m), 898(s), 799(s), 680(m, br). Elution of the compound through a protonated 'Amberlite IR-120'
20 resin column gave a product with a similar ir spectrum (broader peaks) and near identical metal ratio.

17.) Iron containing heteropolytungstates

The structures of these novel compounds are not known. The cations in these products,
25 as is the case for most polyoxometalates, can be exchanged for other cations using standard techniques such as, for example, an appropriate ion exchange resin.

Preparation of compounds 17/1 and 17/2.

30 A solution of 33 g (100 mmol) Na₂WO₄·2H₂O and 2.12 g (10 mmol) Na₂SiO₃·5H₂O in 150 mL H₂O was treated with 6 g (100 mmol) acetic acid and then a solution of 8.1 g (20 mmol) Fe(NO₃)₃·9H₂O in 50 mL H₂O containing 10 g CH₃CO₂Na and 2 mL acetic acid was added drop wise over about 15 - 20 mins. to the

- 11 -

hot reaction solution. After boiling for several hours, the solution was filtered, cooled to room temp. and 20 g KCl added. A yellow-brown solid (5-6 g) separated from the solution. This was recrystallised from hot water to give, after washing with ethanol and air drying, 1.8 g light brown powder. Analysis: %W 48.99, %Fe 9.48, %Si 0.72, %Na 3.75, giving for compound 17/1 an elemental ratio of $W_8Fe_{5.1}Si_{0.78}Na_{4.9}$ (*ie* near $W_8Fe_5SiNa_5$). The pH of the supernatant was reduced to ca. 2.5 with HCl and 20 g $N(n-Bu)_4Cl$ was added. The yellow precipitate (19-20 g) was washed with water and ethanol and air dried. It was then placed in 100 mL H_2O and the pH of the solution was adjusted from 2.5 to 6.9 by the slow addition of 0.05 N KOH. The yellow solution, still containing solids, was filtered and then eluted through an 'Amberlite IR-120' resin column in the K^+ form. On removal of the solvent, 7.2 g of a yellow brown solid was isolated. Analysis: %W 60.20, %Fe 2.02, %Si 1.07, %K 7.31, giving an elemental ratio $W_{18}Fe_{1.99}Si_{2.09}K_{10.3}$ (*ie* near $W_{18}Fe_2Si_2K_{10}$) for compound 17/2. Ir spectrum (KBr disc, cm^{-1}) 1000(w), 960(m), 902(s), 792(s), 730(sh, br.), 680(sh, br).

15

Preparation of compounds 17/3 and 17/4.

27.9 g (90 mmol) of $Na_2WO_4 \cdot 2H_2O$ in 125 mL H_2O was reacted with 1.56 g (10 mmol) $NaH_2PO_4 \cdot 2H_2O$ and the pH of the solution lowered to 8.2 with acetic acid. Then 8.05 g (20 mmol) $Fe(NO_3)_3 \cdot 9H_2O$ dissolved in 40-50 mL H_2O containing ca. 10 g neutralised CH_3CO_2Na was added slowly to the hot (70 - 80°C) reaction solution. After refluxing for several hours, the near clear solution (pH 6.4) was filtered, cooled to room temp., and on addition of 16 g KCl a sticky tan material, which stuck to the bottom of the flask, separated. Then a yellow solid began to separate from the reaction solution and after ca. 1/2 h the solution appeared solid with this yellow material. The yellow material was readily separated from the brown which was adhered to the bottom of the reaction vessel.

The ir of the brown compound showed the PO_4^{3-} stretches as a triplet and also indicated the presence of a nitrate moiety. On recrystallisation from warm water, a flocculant yellow product was obtained and its ir spectrum (KBr disc, cm^{-1}) 1386, 1080, 1057, 1039, 947, 878, 813, 730(br) was very nearly identical to that of the crude material. Analysis: %W 49.69, %Fe 2.82, %P 0.75, %K 10.36 giving the elemental ratio for

30

- 12 -

compound 17/3 of $W_{16}Fe_{2.99}P_{1.43}K_{15.7}$. Since the P analyses (by ICP AES) of many well characterised compounds were often low, the ratio of the above elements in 17/3 may possibly be near $W_{16}Fe_3P_2K_{16}$.

- 5 The ir of the yellow crude material had no NO_3^- peak and only a doublet for the PO_4^{3-} . After recrystallisation from water at $60^\circ C$, the ir spectrum (KBr disc, cm^{-1}) 1076, 1053, 946, 872, 806, 720. Analysis: %W 54.60, %Fe 4.03, % P 0.87, %K 8.20 giving the elemental ratio for compound 17/4 of $W_{16}Fe_{3.89}P_{1.51}K_{11.3}$ (ie near $W_{16}Fe_4P_2K_{11}$).

10 Preparation of compound 17/5.

- 59.4 g (180 mmol) of $Na_2WO_4 \cdot 2H_2O$ in 200 mL H_2O and 2.4 g acetic acid was warmed to $70^\circ C$. A solution of 8.05 g (20 mmol) $Fe(NO_3)_3 \cdot 9H_2O$ in 70 mL H_2O containing also 8 g neutralised CH_3CO_2Na was added to the tungstate solution over 1/2 h, the solution remaining clear, changing colour from yellow near the beginning of the addition to a red brown as the reaction progressed. A solution of $CoCl_2 \cdot 6H_2O$ (9.52 g, 40 mmol) in 70 mL H_2O and 2.4 g acetic acid and containing also 8 g CH_3CO_2Na was added drop wise to the boiling reaction solution over 1 h. Some material precipitated from solution after ca. 5-10 mL of the cobalt solution had been added. The solution was boiled for 1/2 h after addition was complete and then let stand at room temp. over night. Two products were apparent, a greenish material that was washed off the sticky brown compound adhering to the bottom of the vessel. The brown material was dissolved in 300 mL H_2O , filtered through 'Celite' and added 40 g NaCl to the solution. Some more of the greenish material also separated on standing. The brown compound was collected and recrystallised from 100 mL H_2O ($85^\circ C$). The grey brown powder (11.1 g) was analysed; %W 48.92, %Co 6.77, %Fe 2.59, %Na 2.48 giving the elemental ratio for compound 17/5 of $W_7Fe_{1.22}Co_{3.02}Na_{2.8}$.

- 30 In the compounds of formula 1-17, when a transition metal atom(s) replace(s) one or more tungsten atoms in the structure, the oxygen on the transition metal atom(s) may be either doubly protonated (H_2O), singly protonated (OH), or completely deprotonated (O). The acidity of these protons, and the compounds that are obtained,

- 13 -

as is known to one skilled in the art of polyoxometallate chemistry, depends on the nature of the transition metal atom, its oxidation state, the basicity of the polyanion formed and the basicity of the solution from which the compounds were isolated. In the compounds of the invention not all oxygen atoms are necessarily oxo groups and the charge (and hence the number of counter cations (A)) on the polyanion will depend on the number of protons attached to the oxygen atom(s). Furthermore, compounds containing groups such as, for example, MOH, may dimerize by an intermolecular condensation reaction. Dimers, where formed, of the compounds listed, are also included in the invention.

10

Many of the compounds of the invention can occur in a number of isomeric forms. In fact, it is at times difficult to obtain isomerically pure compounds. All isomers or isomer mixtures are included in this invention.

15 Many of the compounds can undergo one or more electron reductions. The reduced compounds are also included in this invention.

The charge on the polyanions can vary, depending upon the extent of protonation of the polyanions, as noted earlier, and upon the oxidation states of the metal atoms. The number of associated counter cations (A) will vary correspondingly. A may be a proton, an alkali metal ion, an alkali earth ion, or ammonium or alkyl ammonium ion of type $R_{4-n}H_nN^+$, where R is an alkyl chain of from 1 to 6 carbon atoms. The required cation is generally introduced into the compound either by use of an ion exchange resin or by precipitation with excess of a salt of that cation.

20

25 It is to be noted that, as one skilled in the art of heteropolyanion chemistry would know, not all combinations of the elements given in formulae 1 to 17 are isolable.

Preparation of Compositions

Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

10 A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. inert diluent, preservative disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) 15 surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release 20 profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Compositions suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured basis, usually sucrose and acacia or 25 tragacanth gum; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia gum; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Compositions for rectal administration may be presented as a suppository with 30 a suitable base comprising, for example, cocoa butter or a salicylate.

- 15 -

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

5 Compositions suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include
10 suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile
15 powders, granules and tablets of the kind previously described.

Preferred unit dosage compositions are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

20 The compounds according to the invention may also be presented for use in the form of veterinary compositions, which may be prepared, for example, by methods that are conventional in the art. Examples of such veterinary compositions include those adapted for:

- (a) oral administration, external application, for example drenches (e.g.
25 aqueous or non-aqueous solutions or suspensions); tablets or boluses; powders, granules or pellets for admixture with feed stuffs; pastes for application to the tongue;
- (b) parenteral administration for example by subcutaneous, intramuscular or intravenous injection, e.g. as a sterile solution or suspension; or (when appropriate) by intramammary injection where a suspension or solution is introduced into
30 the udder via the teat;
- (c) topical application, e.g. as a cream, ointment or spray applied to the skin; or
- (d) intravaginally, e.g. as a pessary, cream or foam.

- 16 -

It should be understood that in addition to the ingredients particularly mentioned above, the compositions of this invention may include other agents conventional in the art having regard to the type of composition in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and

5 flavouring agents.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way. The term "active ingredient" as used in

10 Examples 3 to 6 means one or more compounds of selected from Formulae 1-17 or a pharmaceutically acceptable derivative thereof.

EXAMPLE 1 Compounds of the invention

15

Example active ingredients according to the invention were prepared and analysed by ICP spectroscopy. The compound formula and the analytical results compared with the composition expected from the formula are given in Table 1 below. Ir and nmr data are also included.

20

TABLE 1

Anion Type	Analyses [% found (% calc)]
1	$K_8[P_2V_2W_{16}O_{62}] \cdot 40H_2O$ %W 57.07 (57.33); %V 2.15 (1.99), %K 5.69 (6.10), %P 0.92 (1.21)
1	$K_8[P_2MoV_2W_{15}O_{62}] \cdot 38H_2O$ %W 55.11 (55.08), %V 2.25 (2.03), %Mo 2.17 (1.92), %K 6.14 (6.25), %P 0.93 (1.24)
1	$K_7[P_2Mo_2VW_{15}O_{62}] \cdot 34H_2O$ %W 55.86 (55.82), %V 1.15 (1.03), %Mo 3.07 (3.88), %K 5.73 (5.54), %P 0.92 (1.25)
2	$K_9[P_2MoV_3W_{14}O_{62}] \cdot 45H_2O$ %W 51.54 (51.08), %V 2.87 (3.03), %Mo 1.89 (1.90), %K 7.52 (6.99), %P 0.89 (1.23)
2	$K_6[P_2Mo_4W_{14}O_{62}] \cdot 28H_2O$ %W 54.26 (54.18), %Mo 7.61 (8.08), %K 5.21 (4.94), %P 0.91 (1.30)
3	$K_{18}[Ti_6W_{12}P_2O_{62}] \cdot 35H_2O$ %W 45.39 (45.19), %Ti 5.69 (5.89), %K 13.5 (14.4)
3	$(NH_4)_{18}[Ti_6W_{12}P_2O_{62}] \cdot 35H_2O$ %W 49.07 (49.00), %Ti 6.22 (6.38)
4	$Cs_4[(CH_3CO_2CH_2CH_2Si)_2SiW_{11}O_{40}] \cdot 5H_2O$ %W 57.04 (57.09), %Si 2.05 (2.38)

- 17 -

Anion Type	Analyses [% found (% calc)]
4	$\text{Cs}_4[(\text{NCC}_3\text{H}_6\text{Si})_2\text{SiW}_{11}\text{O}_{40}]\cdot 5\text{H}_2\text{O}$ %W 57.54 (57.54), %Si 2.04 (2.40)
5	$\text{Na}_6[\text{CeW}_{10}\text{O}_{36}\text{H}_2]\cdot 38\text{H}_2\text{O}$ %W 54.88 (54.41), %Ce 3.96 (4.15)
5	$\text{K}_6[\text{NdW}_{10}\text{O}_{36}\text{H}_3]\cdot 38\text{H}_2\text{O}$ %W 55.71 (55.70), %K 7.16 (7.11)
6	$\text{K}_8[\gamma\text{-SiW}_{10}\text{O}_{36}]\cdot 12\text{H}_2\text{O}$ IR(KBr) Main peaks at 989, 942, 905, 865, 818, 740 cm^{-1}
5	7 $\text{K}_{12}\text{H}_2[\text{P}_2\text{W}_{12}\text{O}_{48}]\cdot 24\text{H}_2\text{O}$ IR(KBr, P-O bands); 1130, 1080, 1010, cm^{-1} ^{31}P nmr (D2O) δ -8.38(s) [ref. 85% H_3PO_4]
8	$\text{K}_{28}\text{Li}_5\text{H}_7\text{P}_8\text{W}_{48}\text{O}_{184}\cdot 75\text{H}_2\text{O}$ %W 60.88 (60.84), %K 6.95 (7.55), %P 1.66 (1.71)
9	$\text{Na}_{12}\text{P}_4\text{W}_{14}\text{O}_{58}\cdot 42\text{H}_2\text{O}$ %W 53.35 (53.45), %P 1.50 (1.50)
10	10 $(\text{NH}_4)_{14}[\text{NaP}_5\text{W}_{30}\text{O}_{110}]\cdot 73\text{H}_2\text{O}$ %W 61.1 (61.14), %P 1.74 (1.72)
11	$\text{Na}_{14}\text{H}_6[\text{P}_6\text{W}_{18}\text{O}_{79}]\cdot 58\text{H}_2\text{O}$ %W 53.97 (54.08), %P 2.88 (3.04)
10	11 $\text{Na}_{20}[\text{P}_6\text{W}_{18}\text{O}_{79}]\cdot 50\text{H}_2\text{O}$ %W 53.75 (53.76), %Na 7.50 (7.47), %P 2.61 (3.02)
12	$(\text{NH}_4)_{12}\text{H}_2[\text{La}_4(\text{MoO}_4)(\text{H}_2\text{O})_{16}(\text{Mo}_7\text{O}_{24})_4]\cdot 54\text{H}_2\text{O}$ %Mo 42.85 (43.36), %La 9.41 (8.66)
12	$(\text{NH}_4)_{12}\text{H}_2[\text{Eu}_4(\text{MoO}_4)(\text{H}_2\text{O})_{16}(\text{Mo}_7\text{O}_{24})_4]\cdot 52\text{H}_2\text{O}$ %Mo 43.32 (43.25), %Eu 9.37 (9.45)
13	$((\text{CH}_3)_4\text{N})_{12}\text{H}_4\text{P}_4\text{W}_y\text{Nb}_6\text{O}_{123}\cdot 110\text{H}_2\text{O}$ %W 50.82 (49.96), %Nb 4.96 (5.06), %P 0.90 (1.12)
14	$\text{K}_7\text{H}_2\text{PV}_{14}\text{O}_{42}\cdot 16\text{H}_2\text{O}$ %V 35.88 (36.02), %K 14.16 (13.82)
15	14 $(\text{NH}_4)_7\text{H}_2[\text{PV}_{14}\text{O}_{42}]\cdot 8\text{H}_2\text{O}$ %V 42.46 (42.24), %P 1.10 (1.83)
15	15 $\text{Na}_3\text{H}_9[\text{PV}_{13}\text{O}_{41}]\cdot 22\text{H}_2\text{O}$ %V 36.34 (36.32), %Na 3.55 (3.78)
16/1	See preparation details
16/2	See preparation details
16/3	See preparation details
20	17/1 See preparation details
17/2	See preparation details
17/3	See preparation details
17/4	See preparation details
25	17/5 See preparation details

- 18 -

EXAMPLE 2: Antiviral Activity

The compounds listed in Example 1 were tested for their ability to inhibit RNA synthesis in an *in vitro* polymerase assay (Chu and Westaway, 1985, 1987; Brun and Brinton, 1986). In this assay, flavivirus RNA comprising the genomic 44S RNA, a double-stranded replicative form (RF) and a partially-double-stranded replicative intermediate (RI) are detected by the incorporation of [α -³²P]GTP.

A. *Preparation of virus-infected Vero cell extracts*

10

Vero cells were infected at a multiplicity of infection of 7 for Type 2 dengue (DEN-2) virus (New Guinea C strain; Sabin and Schlesinger, 1945) or Kunjin (KUN) virus (strain MRM 61C; Boulton and Westaway, 1972). Extracts containing RNA-dependent RNA polymerase (RDRP) activity derived from DEN-2 virus-infected cells were prepared at 30 to 36 h p.i., when polymerase activity was at a maximum. Similarly, extracts of KUN virus-infected cells were prepared at the time of maximum polymerase activity at 24 h p.i. (Chu and Westaway, 1985).

The cells were pelleted by centrifugation and resuspended in 10 mM sodium acetate at a concentration of 2×10^7 cells/ml. They were then disrupted by passaging 20 times through a 21 gauge needle followed by 20 times through a 26 gauge needle. The disrupted cells were centrifuged at 800 g for 7 min to obtain a supernatant fraction and a pellet of the nuclear-associated material. All RDRP assays were performed using the supernatant fraction, hereafter referred to as the cell extract, which was stored at -70°C and used after only one cycle of freeze/thawing.

B. *RNA-dependent RNA polymerase assay*

The RDRP activity in the cell extract was assayed as previously described with the following modifications (Chu and Westaway, 1985). In each RDRP assay the virus-infected cell extract contained 4.5-6 mg/ml of protein. The compound to be tested dissolved in double distilled water and RNasin (0.5 units/ml, Promaga) were

- 19 -

added to the cell extract for 10 min prior to the addition of the other components of the RDRP assay. The final reaction mixture (total volume of 50 μ l) contained 50 mM Tris-HCl pH 8.0, 10 mM magnesium acetate, 7.5 mM potassium acetate, 10 mM 2-mercaptoethanol, 6 μ g actinomycin D (AMD), 5 mM phosphoenolpyruvate, 3 units/ μ l pyruvate kinase, 0.5 mM ATP, 0.5 mM CTP, 0.5 mM UTP, 25 μ M GTP, 5 μ Ci [α -³²P] GTP (Amersham, specific activity 410 Ci/mmol), 0.5 units/ml RNasin, 30 μ l of infected cell extract and the test compound (from 0.5 to 100 μ M). The reaction was stopped after 30 min at 37°C by the addition of EDTA to a final concentration of 10 mM. An equal volume of TNE-SDS (50 mM Tris-acetate pH 7.6, 0.1 M sodium acetate, 1 mM EDTA and 2% SDS) was added to disrupt membranes. The RNA was then extracted with phenol and precipitated by ethanol.

C. Electrophoresis of RNA

RNA samples were mixed with an equal volume of sample buffer containing 7 M urea in TBE (89 mM Tris-HCl, 89 mM boric acid, 2.5 mM EDTA) and 0.5% bromophenol blue, and were separated by electrophoresis through 3% polyacrylamide gels containing 7 M urea in TBE. The gels were fixed in 10% acetic acid, dried and radiolabelled bands detected by autoradiography.

20 Results

The compounds tested inhibited the synthesis of both DEN-2 and KUN RF RNA. There was also a decrease in the amount of RI detected with increasing concentration of drug. The concentrations which give >75% inhibition of RNA synthesis are given in Table 2.

25


References

- BOULTON, R.W. AND WESTAWAY, E.G. (1972).
Comparisons of Togaviruses: Sindbis virus (Group A) and Kunjin virus (Group B). *Virology* 49, 283-289.
- 5
- CHU, P.W.G. AND WESTAWAY, E.G. (1985).
Replication strategy of Kunjin virus: evidence for recycling, role of the replicative form RNA as template in semiconservative and asymmetric replication. *Virology* 140, 68-79.
- 10
- CHU, P.W.G. AND WESTAWAY, E.G. (1987).
Characterization of Kunjin virus RNA-dependent RNA polymerase: reinitiation of synthesis in vitro. *Virology* 157, 330-337.
- 15
- GRUN, J.B. AND BRINTON, M.A. (1986).
Characterisation of West Nile virus RNA-dependent RNA polymerase and cellular adenylyl and uridylyl transferases in cell-free extracts. *Journal of Virology* 60, 1113-1124.
- 20
- SABIN, A.B. AND SCHLESINGER, R.W. (1945).
Production of immunity to dengue with virus modified by propagation in mice. *Science* 101, 640-642.

The compounds were dissolved in doubly distilled water and tested as described above. The compounds tested and their antinflavi-viral activity are given in the Table 2 below.

5

Table 2



Anion type	Molecular Formula	Inhibitory Conc. (μM) (RDRP)
1	$K_6[P_2V_2W_{16}O_{62}].40H_2O$	5-10
1	$K_8[P_2MoV_2W_{15}O_{62}].38H_2O$	>100
1	$K_7[P_2Mo_2VW_{15}O_{62}].34H_2O$	10-50
2	$K_9[P_2MoV_3W_{14}O_{62}].45H_2O$	10-50
2	$K_6[P_2Mo_4W_{14}O_{62}].28H_2O$	10-50
3	$K_{18}[Ti_6W_{12}P_2O_{62}].35H_2O$	
3	$(NH_4)_{18}[Ti_6W_{12}P_2O_{62}].35H_2O$	
4	$K_4[C_5H_5TiPW_{11}O_{39}].nH_2O$	50-100
5	$Na_6[CeW_{10}O_{36}H_2].38H_2O$	>100
8	$K_{28}Li_5H_7P_8W_{48}O_{184}.75H_2O$	>10
9	$Na_{12}P_4W_{14}O_{58}.42H_2O$	75-100
10	$(NH_4)_{14}[NaP_5W_{30}O_{110}].nH_2O$	5
11	$Na_{14}H_6[P_6W_{18}O_{79}].nH_2O$	10
11	$Na_{20}[P_6W_{18}O_{79}].nH_2O$	5
14	$K_7H_2PV_{14}O_{42}.16H_2O$	50
14	$(NH_4)_7H_2[PV_{14}O_{42}].8H_2O$	50
15	$Na_3H_9[PV_{13}O_{41}].22H_2O$	5
16/1	$K_8H_8[(Zr_3SiW_9O_{40})_2Zr].40H_2O$	5
16/2	$K_{12}[Zr(Zr_2W_{10}SiO_{40})_2].38H_2O$	
16/3	$K_{12}[Zr(Zr_2SiW_{10}O_{40})_2].74H_2O$	
17/1	$Na_5Fe_5W_8SiO_{36}.29H_2O$	1-5
17/2	$K_{10}[Fe_2(H_2O)_4(SiW_9FeO_{34}H_3)_2].26H_2O$	10-50
17/3	$K_{16}[Fe(NO_3)(PW_8FeO_{34}H_3).54H_2O$	1-5
17/4	$K_{12}[Fe_2(H_2O)_4(PW_8FeO_{34}H_3)_2].32H_2O$	1-5
17/5	$Na_6HCo_6Fe_2W_{14}O_{60}.62H_2O$	1-5

- 22 -

EXAMPLE 3: Tablet Formulations

- 5 The following formulation A may be prepared by wet granulation of the ingredients with a solution of povidone, followed by addition of magnesium stearate and compression.

		<u>mg/tablet</u>	
10	<u>Formulation A</u>		
	(a) Active ingredient	250	250
	(b) Lactose B.P.	210	26
	(c) Povidone B.P.	15	9
	(d) Sodium starch glycollate	20	12
15	(e) Magnesium stearate	5	3
		500	300

- The following formulation B, may be prepared by direct
 20 compression of the admixed ingredients.

	<u>Formulation B</u>	<u>mg/capsule</u>
	Active ingredient	250
	Pregelatinised starch NF15	150
25		400

Formulation C (Controlled release formulation)

- This formulation may be prepared by wet granulation of the
 30 ingredients (below) with a solution of povidone followed by the addition of magnesium stearate and compression.

	<u>mg/tablet</u>
(a) Active ingredient	500
(b) Hydroxypropylmethylcellulose	112

- 23 -

(methocel K4M Premium)

(c)	Lactose B.P.	53
(d)	Povidone B.P.C.	28
(e)	Magnesium stearate	7

5

700

EXAMPLE 4: Capsule Formulations**10 Formulation A**

A capsule formulation may be prepared by admixing the ingredients of Formulation B in Example 3 above and filling into a two-part hard gelatin capsule. Formulation B (*infra*) may be prepared in a similar manner.

15

Formulation B

		<u>mg/capsule</u>
	(a) Active ingredient	250
	(b) Lactose B.P.	143
20	(c) Sodium starch glycollate	25
	(d) Magnesium stearate	2
		420

Formulation C (Controlled release capsule)

25

The following controlled release capsule formulation may be prepared by extruding ingredients a, b and c using an extruder, followed by spheronisation of the extrudate and drying. The dried pellets may then be coated with release-controlling membrane (d) and filled into a two-piece,
30 hard gelatin capsule.

		<u>mg/capsule</u>
	(a) Active ingredient	250
	(b) Microcrystalline cellulose	125

- 24 -

(c)	Lactose B.P.	125
(d)	Ethyl cellulose	13

513

5

EXAMPLE 5: Injectable FormulationFormulation:

10	Active ingredient	0.200 g
	Hydrochloric acid solution, 0.1M	qs to pH 5.0-7.0
	Sodium hydroxide solution, 0.1M	qs to pH 5.0-7.0
	Sterile water	qs to 10 ml

- 15 The active ingredient may be dissolved in most of the water (35°-40°C) and the pH adjusted to between 5.0 and 7.0 with the hydrochloric acid or the sodium hydroxide as appropriate. The batch may then be made up to volume with the water and filtered through a sterile micropore filter into a sterile 10 ml amber glass vial (type 1) and sealed with sterile closures
- 20 and overseals.

- Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a
- 25 stated integer or group of integers but not the exclusion of any other integer or group of integers.

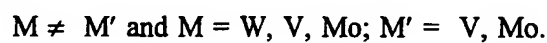
- 25 -

CLAIMS:

1. A method for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises the administration to a patient in
 5 need of such treatment or prophylaxis of an effective amount of one or more compounds selected from Formulae 1 to 17 and dimers, isomers, solvates or reduced forms thereof:



10 wherein

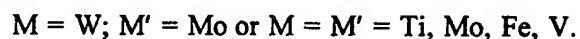


wherein

15 $M, M' = V, Mo.$



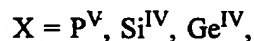
wherein



20



wherein



R = an organic residue or one containing an organometallic, metal
 25 carbonyl or metal coordinated with a ligand,

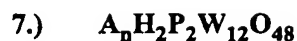


wherein

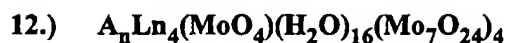
30 $M = \text{lanthanoid}, Zr^{IV}.$



- 26 -

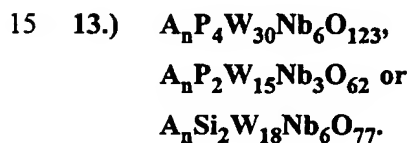


10



wherein

Ln = lanthanoid metal ion.



20



16.) Zirconium containing heteropolytungstates.

17.) Iron containing heteropolytungstates.

25

and wherein in each of the above formulae, A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule; or pharmaceutically acceptable derivatives thereof.

- 30 2. A method as claimed in Claim 1, characterised in that A is a proton, an alkali metal, alkaline earth or ammonium cation, or an alkylammonium cation of the formula $R_{4-m} H_m N^+$, where R is an alkyl chain of from 1 to 6 carbon atoms and m is 0, 1, 2 or 3.

- 27 -

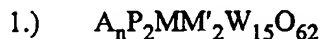
3. A method as claimed in Claim 1 or Claim 2, characterised in that the compound is administered in the form of a pharmaceutical composition which comprises the said compound in association with a pharmaceutically acceptable carrier or diluent.

5

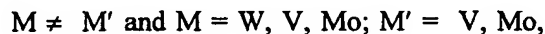
4. The use in the manufacture of a medicament for the treatment or prophylaxis of a flavivirus associated infection of a compound as defined in Claim 1 or Claim 2.

10 5. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises a compound as defined in Claim 1 or Claim 2, in association with a pharmaceutically acceptable carrier or diluent.

15 6. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 1 or dimers, isomers, solvates or reduced forms thereof:



20 wherein



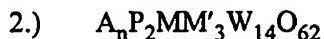
A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;

or pharmaceutically acceptable derivatives thereof.

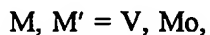
25

7. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 2 or dimers, isomers, solvates or reduced forms thereof:

30



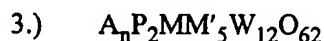
wherein



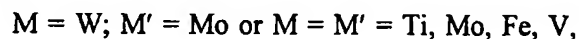
- 28 -

A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;
or pharmaceutically acceptable derivatives thereof.

- 5 8. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 3 or dimers, isomers, solvates or reduced forms thereof:



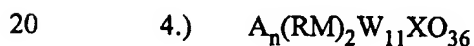
10 wherein



A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;
or pharmaceutically acceptable derivatives thereof.

15

9. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 4 or dimers, isomers, solvates or reduced forms thereof:



wherein



R = an organic residue or one containing an organometallic, metal carbonyl or metal coordinated with a ligand

- 25 A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;
or pharmaceutically acceptable derivatives thereof.

10. A pharmaceutical composition for the treatment or prophylaxis of a
30 flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 5 or dimers, isomers, solvates or reduced forms thereof:



- 29 -

wherein

$M = \text{lanthanoid, Zr}^{\text{IV}},$

A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;

5 or pharmaceutically acceptable derivatives thereof.

11. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 6 or dimers, isomers, solvates or reduced forms

10 thereof:



wherein A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;

or pharmaceutically acceptable derivatives thereof.

15

12. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 7 or dimers, isomers, solvates or reduced forms thereof:



wherein A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;

or pharmaceutically acceptable derivatives thereof.

25 13. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 8 or dimers, isomers, solvates or reduced forms thereof:



30 wherein A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;

or pharmaceutically acceptable derivatives thereof.

- 30 -

14. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 9 or dimers, isomers, solvates or reduced forms thereof:



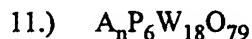
wherein A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;
or pharmaceutically acceptable derivatives thereof.

10 15. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 10 or dimers, isomers, solvates or reduced forms thereof:



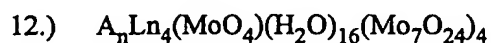
15 wherein A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;
or pharmaceutically acceptable derivatives thereof.

16. A pharmaceutical composition for the treatment or prophylaxis of a
20 flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 11 or dimers, isomers, solvates or reduced forms thereof:



25 wherein A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;
or pharmaceutically acceptable derivatives thereof:

17. A pharmaceutical composition for the treatment or prophylaxis of a
30 flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 12 or dimers, isomers, solvates or reduced forms thereof:



wherein

- 31 -

Ln = lanthanoid metal ion,

A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;

or pharmaceutically acceptable derivatives thereof.

5

18. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 13 or dimers, isomers, solvates or reduced forms thereof:

10 13.) $A_nP_4W_{30}Nb_6O_{123}$

$A_nP_2W_{15}Nb_3O_{62}$

$A_nSi_2W_{18}Nb_6O_{77}$

wherein A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;

15 or pharmaceutically acceptable derivatives thereof.

19. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 14 or dimers, isomers, solvates or reduced forms thereof:

20

14.) $A_nPV_{14}O_{42}$

wherein A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;

or pharmaceutically acceptable derivatives thereof.

25

20. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises one or more compounds of Formula 15 or dimers, isomers, solvates or reduced forms thereof:

30 15.) $A_nPV_{13}O_{41}$

wherein A is a cation and n is the number of such cations necessary for electrical neutrality of the molecule;


or pharmaceutically acceptable derivatives thereof.

- 32 -

21. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises one or more zirconium containing heteropolytungstates or dimers, isomers, solvates or reduced forms thereof, or pharmaceutically acceptable derivatives thereof.

5

22. A pharmaceutical composition for the treatment or prophylaxis of a flavivirus associated infection, characterised in that it comprises one or more iron containing heteropolytungstates or dimers, isomers, solvates or reduced forms thereof, or pharmaceutically acceptable derivatives thereof.

A. CLASSIFICATION OF SUBJECT MATTER Int. Cl. ⁶ A61K 33/24 According to International Patent Classification (IPC) or to both national classification and IPC					
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC : A61K 33/24 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched AU : IPC as above Electronic data base consulted during the international search (name of data base, and where practicable, search terms used) WPAT TUNGST: POLYTUNGST, LANTH: POLYLANTH, CASM VANAD: POLYVANAD, MOLY: POLYMOLY, FLAVIVIR					
C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.			
P,X	AU 55545/94 (COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION) 9 June 1994 (09.06.94) whole document	1-16, 18, 21, 22			
P,X	AU 42555/93 (COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION) 11 November 1993 (11.11.93) whole document	1-16, 18, 21, 22			
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex. </div>					
<table style="width: 100%; border: none;"> <tr> <td style="width: 33%; vertical-align: top;"> * Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td style="width: 33%; vertical-align: top;"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family </td> <td style="width: 33%;"></td> </tr> </table>			* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family	
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family				
Date of the actual completion of the international search 30 January 1995 (30.01.95)	Date of mailing of the international search report 7 Feb 1995 (7.2.95)				
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. 06 2853929	Authorized officer  J.P. PULVIRENTI Telephone No. (06) 2832251				

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate of the relevant passages	Relevant to Claim No.
X A	EP,A 390365 (JOHNSON MATTHEY PLC) 3 October 1990 (03.10.90) claims page 7	4-16, 18, 21, 22 1-3, 17, 19, 20
X A	EP,A 442663 (JOHNSON MATTHEY PLC) 21 August 1991 (21.08.91) claims, examples	4-16, 18, 21, 22 1-4, 17, 19, 20
X A	EP,A 450065 (TERUMO K.K. et al) 9 October 1991 (09.10.91) claims, page 4	4-16, 18, 21, 22 1-3, 17, 19, 20
X A	WO,A, 92/09292 (JOHNSON MATTHEY PLC) 11 June 1992 (11.06.92) whole document	4-16, 18, 21, 22 1-3, 17, 19, 20
X A	GB 1385489 (AGENCE NATIONALE DE VALORISATION DE LA RECHERCHE) 26 February 1975 (26.02.75)	4-16, 18, 21, 22 1-3, 17, 19, 20

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
AU	55545/94	WO	9412192		
AU	42555/93	WO	9321934		
EP	390365	AU	51410/90	EP	390365
		JP	3047130	US	5093134
EP	442663	AU	70944/91	GB	9003430
EP	450065	AU	28220/89	JP	4211016
WO	9209292	WO	9006756	JP	1038022
		AU	90299/91	GB	9025847
GB	1385489	BE	776565		
END OF ANNEX					